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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,824	02/27/2001	David J Squirrell	BJS-1498-119	3738

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EXAMINER	
STEADMAN, DAVID J	
ART UNIT	PAPER NUMBER
1656	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/03/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/763,824	SQUIRRELL ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *86-105* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *86-105* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/16/07 has been entered.

[2] Claims 86-105 are pending in the application.

[3] Applicant's amendment to the claims, filed on 1/16/07, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[4] Applicant's amendment to the specification, filed on 1/16/07, is acknowledged. It is noted that applicant states, "[t]he specification has been revised to include the attached Sequence Listing" (instant response at p. 8, middle). However, the examiner can find no sequence listing attached to the instant response. Clarification is requested.

[5] Applicant's arguments filed on 1/16/07 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[6] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Objections

[7] Claim 86 is objected to in the recitation of "amino Thr-214" in line 6. It is suggested that "acid" be inserted following "amino" in the noted phrase.

[8] Claim 105 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The polypeptide of claim 104 appears to be limited to a protein comprising SEQ ID NO:37 with a single mutation at position 214 to replace Thr with Cys, Ala, or Asn. However, claim 105 is drawn to the polypeptide of claim 104 with at least one additional mutation and consequently, does not further limit the polypeptide of claim 104.

Claim Rejections - 35 USC § 112, Second Paragraph

[9] Claims 87, 89, and 104-105 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claim 87 (claim 89 dependent therefrom) is confusing in the recitation of "SEQ ID NO:38" as the most recent sequence listing filed on 2/21/06 fails to include a sequence identified as SEQ ID NO:38. It is suggested that applicant clarify the meaning of the claim.

[b] Claim 104 recites "the recombinant protein comprises SEQ ID NO:37 with the proviso that the amino acid residue corresponding to Thr-214 of SEQ ID NO:37" and

claim 105 recites ""[t]he recombinant protein of claim 104, wherein the amino acid residue corresponding to Thr-214 of SEQ ID NO:37" (emphasis added). In this case, the amino acid at position 214 of SEQ ID NO:37 is necessarily a threonine residue. However, in view of the recitation of "corresponding to" it is unclear as to whether the residue at position 214 of SEQ ID NO:37 is or is not intended as being a threonine. It is suggested that applicant clarify the meaning of the claims.

[c] The polypeptide of claim 104 appears to be limited to a protein comprising SEQ ID NO:37 with a single mutation at position 214 to replace Thr with Cys, Ala, or Asn. However, claim 105 is drawn to the polypeptide of claim 104 with at least one additional mutation. As such, claim 105 is confusing as it is unclear as to how the polypeptide of claim 104, which appears to be limited as noted above, can simultaneously have at least one additional mutation at the noted position(s). It is suggested that applicant clarify the meaning of claim 105. According to 37 CFR 1.75, "[c]laims in dependent form shall be construed to include all the limitations of the claim incorporated by reference into the dependent claim." In the interest of advancing prosecution, the sequence of the polypeptide of claim 105 has been interpreted as being limited to comprising SEQ ID NO:37, except that Thr at position 214 is replaced with Cys, Ala, or Asn, and at least one of mutations (a)-(f) is present.

Claim Rejections - 35 USC § 112, First Paragraph

[10] Claims 91 and 105 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

MPEP § 2163 states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims" and "[i]f the originally filed disclosure does not provide support for each claim limitation, or if an element which applicant describes as essential or critical is not claimed, a new or amended claim must be rejected under 35 U.S.C. 112, para. 1, as lacking adequate written description."

Claim 91 requires that the claimed protein consist of 550 amino acids, which is a narrowing limitation. According to applicant, support for claim 91 can be found in original claim 1. However, the examiner can find no support for the limitation requiring the protein to consist of 550 amino acids in original claim 2 or in the specification or claims as originally filed.

Claim 105 is requires a mutation at position 214 of SEQ ID NO:37 and at least one other mutation at position(s) 14, 35, 215, 232, 295, and/or 354 with the specifically recited amino acids. According to applicant, support for the claim can be found at pp. 14-15 and Examples 2-4 and 7. While the specification at pp. 14-15 supports specific species of SEQ ID NO:37, this support fails to support any combination of mutations as encompassed by the claim. For example, this disclosure would appear to fail to support a 214/354 double mutant.

Applicant is invited to show support the limitations at issue.

[11] The written description rejection of claims 67-85 under 35 U.S.C. 112, first paragraph, is withdrawn in view of applicant's amendment to cancel the claims. The rejection is herein applied to newly added claims 86-105. The written description rejection of claims 86-105 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action.

RESPONSE TO ARGUMENT: Applicant argues the genus of claimed proteins and nucleic acids is described by both structural and functional limitations as encompassed by the claims. Applicant argues the specification discloses representative species of the claimed genus and, in view of the knowledge of luciferases and recombinant protein production at the time of the invention, this is sufficient to show possession of the claimed genus. Applicant points to the "Revised Interim Written Description Guidelines Training Materials" which states that a single representative species may be sufficient to describe a genus (p. 31, top) and further points to Example 14 at pp. 53-55, which sets forth the following claim: "[a] protein having SEQ ID NO: 3 and variants thereof that are at least 95% identical to SEQ ID NO: 3 and catalyze the reaction of A→ B" and states that a single disclosed species is sufficient to describe the claimed genus. By analogy, applicant argues, the disclosed species describes the claimed genus of proteins and nucleic acids. Applicant argues the term "similarity" is described in the specification and a skilled artisan would recognize how to determine those sequences which have the recited "similarity." While applicant acknowledges differences between the claims of this application and the claim of Example 14 of the

Guidelines, applicant argues these differences do not limit the applicability of Example 14 to the instant claims. Applicant further argues the genus is adequately described in the view of a "Decision Tree" of the Guidelines.

Applicant's argument is not found persuasive. The examiner acknowledges that the genus of claimed proteins and nucleic acids is described by the structural feature of being 90% similar to SEQ ID NO:37, having mutation at position 214, and having the function of luciferase and increased thermostability. The issue is whether the disclosed species adequately describe all members of the claimed genus, which encompasses any protein from any source having the recited 90% similarity to SEQ ID NO:37 or which is encoded by a nucleic acid that hybridizes to SEQ ID NO:38 or a nucleic acid encoding SEQ ID NO:37 under conditions recited in claims 87-88 and having the recited functional characteristics. While applicant argues that by analogy to Example 14, the claimed genus is adequately described. However, in contrast to the instant claims which are drawn to variants having "at least 90% similarity to...SEQ ID NO:37" (emphasis added), the structures of the proteins of the claim of Example 14 are limited to those that are "at least 95% identical to SEQ ID NO:3" (emphasis added). Thus, there are at least two differences between the Example 14 claim and the instant claims: 1) the numerical percentage limitation, *i.e.,* 90% and 95%, and 2) the method of sequence comparison, *i.e.,* identity and similarity. Claims 87-88 have a difference 3), particularly as the sequences are structurally limited by hybridization. While the examiner recognizes that certain differences are likely to exist between any two cases, it is the examiner's position that the noted differences are critical in holding lack of adequate

written description. In Example 14 of the Guidelines, a single species is found to represent the genus of variants that have at least 95% identity thereto and share a defined enzymatic activity. While the claimed polypeptides of this case share a common activity, *i.e.,* luciferase activity, the claims of the instant case allow for at least 90% similarity to SEQ ID NO:37. Focusing on the numerical percentage identity, while the percentage identity is increased overall by only 5%, this increases the allowed variation relative to SEQ ID NO:37 by 100%, *i.e.,* 10% is 100% greater than 5%. Moreover, because an identity comparison allows for no mismatches, while similarity does, the variation is even greater. Put another way, a sequence that is 90% identical to a reference sequence can have an even lower similarity, *e.g.,* 85% to the reference sequence. While the "Decision Tree" at p. 17 of the response is noted, this Decision Tree appears to be more relevant to the determination of whether a new claim introduces new matter. A Decision Tree that appears to be more relevant to the instant claims is that at p. 9 of the Guidelines. While the examiner acknowledges certain disclosed species of the claimed variant luciferase polypeptides, it is the examiner's position, in view of the limitation that allows for "at least 90% similarity to SEQ ID NO:37" or hybridization under the recited hybridization conditions of claims 87-88, the disclosed species fail to reflect the variation among members of the genus, which encompasses widely variant structures. Regarding applicant's remark that a single species may be sufficient to describe a genus, MPEP § 2163 makes clear that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species

within the genus" and the Court recognizes that the biological arts are unpredictable. See *Mycogen Plant Science Inc. v. Monsanto Co.*, 58 USPQ2d 1030 (CAFC 2001).

Thus, at least for the reasons of record and the reasons stated above, the examiner maintains that the specification fails to adequately describe all members of the claimed genus of proteins and nucleic acids as encompassed by the claims.

[12] The scope of enablement rejection of claims 67-85 under 35 U.S.C. 112, first paragraph, is withdrawn in view of applicant's amendment to cancel the claims. The rejection is herein applied to newly added claims 86-105. The written description rejection of claims 86-105 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action.

RESPONSE TO ARGUMENT: Applicant argues: 1) numerous working examples of the claimed invention are disclosed; 2) sufficient guidance is disclosed in the specification regarding the making, testing, and using of variants encompassed by the claims to enable a skilled artisan to make the use the full scope of the claimed invention without undue experimentation; 3) the examiner focuses only on the level of predictability in the art instead of considering all relevant Factors of *In re Wands,* which is reinforced by *Capon v. Eshhar v. Dudas;* 4) inventions in the biological sciences may have "some unpredictability" as evidenced by issued US patents and the "Revised Interim Written Description Guidelines Training Materials."

Applicants' argument is not found persuasive. While it is acknowledged that the examiner's remarks addressing the instant rejection in the 9/19/2005 Office action focus on the level of predictability in the art, this was *necessitated* by applicant's arguments in the response filed on 4/15/2005, which also focus on this Factor of *In re Wands*. Contrary to applicant's argument and in accordance with MPEP § 2164.04, which states "it is not necessary to discuss each factor in the written enablement rejection" and that "[t]he language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims," the examiner *has* addressed all relevant Factors of *In re Wands* in a prior Office action (see particularly pp. 12-16 of the Office action mailed on 12/15/2004). A summary of the relevant Factors follows. Regarding the breadth of the claims, the claims are so broad as to encompass all "recombinant" proteins having "at least 90% similarity" to SEQ ID NO:37 or which is encoded by a nucleic acid that hybridizes to SEQ ID NO:38 or a nucleic acid encoding SEQ ID NO:37 under conditions recited in claims 87-88, mutation at position 214, and having luciferase activity and increased thermostability. In this case, the claims encompass numerous variants of SEQ ID NO:37 that have the recited luciferase activity and increased thermostability, which is undisputed by applicant. The examiner acknowledges the specification's disclosure of the working examples of SEQ ID NO:37 with mutation at position 214 and optionally position 215, 232, and/or 354 and general guidance for creating variants and

methods for testing the resulting variants for luciferase activity and increased thermostability. However, as noted in a prior Office action, the functional effect(s) of altering the amino acid sequence of a polypeptide are *highly* unpredictable, which is undisputed by applicant, and is supported by the prior art (see p. 15 of the Office action mailed on and p. 9 of the Office action mailed on 9/19/2005). The level of unpredictability is further compounded by the requirement of the claims that require not only the encoded protein maintain luciferase activity, but also that it have increased thermostability. Neither the specification nor the prior art provide any expectation that the corresponding mutation at position 214 of SEQ ID NO:37 in other luciferase polypeptides from other sources will have the desired effect of: a) maintaining luciferase activity and b) increasing thermostability and, other than the specifically disclosed working examples, there is no expectation that additional mutations will not deleteriously affect luciferase activity and/or thermostability. The high level of unpredictability is further supported by the references of Sung et al. (*Photochem Photobiol* 68:749-753, 1998, abstract only; cited in the Office action mailed on 5/16/06) and Law et al. (*Biochem J* [Epub ahead of print], 3/21/2006, abstract only; cited in the Office action mailed on 5/16/06), which were published after the earliest effective filing date of the instant application. Sung et al. discloses that mutations at the first 11 amino acids of the N-terminus of *P. pyralis* luciferase are important to the stability of the enzyme, showing that various N-terminal substitutions significantly reduce luciferase activity, while Law et al. discloses that substitution of position 14 of *P. pyralis* luciferase improves thermostability and retain the specific activity of the wild-type enzyme. Put another way,

the art recognizes that a mutation may maintain a desired activity or it may abolish that activity – there is no way to predict such effects. While methods of altering the sequence of a polypeptide were known in the art at the time of the invention, it was not routine to make all variant proteins as encompassed by the claims having a *substantial* number of modifications without the necessary guidance and screen those variants for those having luciferase activity and increased thermostability as encompassed by the claims. Thus, in view of the broad scope of the claims, the lack of guidance and working examples, the high level of unpredictability, and the amount of non-routine experimentation required, the examiner maintains the position that undue experimentation is required to make the full scope of claimed proteins and nucleic acids.

Regarding applicant's argument relying upon issued US patents, applicant is reminded that each application is examined on its merits. That a claim has been determined to satisfy the enablement requirement is not only a consideration of the claim language itself, but also the underlying facts of each application. Regarding applicant's argument relying upon the "Revised Interim Written Description Guidelines Training Materials" for demonstrating enablement, it is noted that MPEP § 2164 states, "[t]he enablement requirement of 35 U.S.C. 112, first paragraph, is separate and distinct from the description requirement."

Double Patenting Rejection(s)

[13] The provisional obviousness-type double patenting rejection of claims 67-85 as being unpatentable over claims 1-4, 6-10, 14-19, 21, 24-26, and 29-37 of co-pending

Application No. 10/111,723 is withdrawn in view of applicant's amendment to cancel the claims. The provisional rejection is herein applied to newly added claims 86-105 for the reasons of record, particularly that the specification of the co-pending '723 application supports an embodiment of claims 1-4, 6-10, 14-19, 21, 24-26, and 29-37 that would anticipate claims 86-105 herein, *i.e.*, Example 12 at pp. 42-43, which teaches a 214C/354K/357F *P. pyralis* luciferase mutant. The provisional rejection was fully explained in a prior Office action.

RESPONSE TO ARGUMENT: Applicant argues the rejection is moot "in view of the above." However, this is not found persuasive because the co-pending '723 application supports an embodiment of claims 1-4, 6-10, 14-19, 21, 24-26, and 29-37 that would anticipate claims 86-105 herein.

Claim Rejections - 35 USC § 102

[14] Claims 87-88 are rejected under 35 U.S.C. 102(e) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Wood et al. (US Patent Application Publication 2003/0068801). Claims 87-88 are drawn to recombinant proteins having luciferase activity and increased thermostability and are encoded by a nucleic acid that hybridizes to SEQ ID NO:38 or a nucleic acid encoding SEQ ID NO:37 under hybridization conditions recited in claims 87-88. Initially, it is noted that the claims fail to recite wash conditions that would remove any non-specifically bound nucleic acids. Also, it is noted that the claims do not require that the nucleic acid encoding the claimed recombinant polypeptide hybridize to the full length of SEQ ID NO:38 or a nucleic acid

encoding SEQ ID NO:37 and thus in accordance with MPEP 2111.01, the claim is interpreted as encompassing a nucleic acid encoding a recombinant protein, wherein only a fragment of the nucleic acid hybridizes to SEQ ID NO:38 or a nucleic acid encoding SEQ ID NO:37.

The reference of Wood et al. teaches thermostable *P. pennsylvanica* luciferase polypeptides of SEQ ID NO:27-28, 30, and 32-33. For a representative alignment with SEQ ID NO:32, see Appendix B of the Office action mailed 12/15/2004.

According to applicant, "[t]he luciferases show remarkable conversation, especially in key conserved regions of their structure" (instant response at p. 11, top). Thus, in the absence of a wash step to remove non-specifically bound nucleic acid and in view of applicant's assertion that the luciferases show "remarkable conservation," it is the examiner's position that at least a portion of the nucleic acids encoding the mutant polypeptides of Wood et al. would at least instantaneously hybridize to SEQ ID NO:38 or a nucleic acid encoding SEQ ID NO:37. This anticipates claims 87-88 as written.

Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.

Conclusion

[15] Status of the claims:

Claims 86-105 are pending.

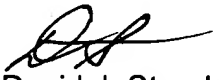
Claims 86-105 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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